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EDITORIAL

Animal experiments and the development of surgical therapies

Experimental animals have played a crucial role in understanding fundamental biology, disease mechanisms and the development and safety testing of new medicines and surgical approaches. Some of those who object to the use of animals argue that animals have played little role in the development of new medical and surgical treatments, or have even hampered progress. This view is difficult to justify in light of the vast weight of evidence to the contrary. Even a brief summary of the development of surgical therapies reveals the contribution of animal research.

The division between medical and surgical research is often blurred; for example, the discovery of insulin, a medical treatment, was done surgically, by Banting and Best, using dogs, but the discovery of the H_2 receptor antagonists, by Sir James Black, removed the treatment of gastrointestinal ulcers from the domain of the surgeon to that of the physician.

Early history

Galen's concept of the shuttlewise ebb and flow of blood held sway for 14 centuries, until William Harvey (1578–1657) discovered that blood circulates. He demonstrated this on small animals such as snakes and rabbits.[1] A century later, Stephen Hales, vicar of Teddington, England, fastened a glass tube inside a horse's artery, thereby discovering and measuring blood pressure, the capacity of the heart, and the flow rate in vessels.

Until the middle of the 19th century, operative surgery consisted mainly of cataract removal, cutting for bladder stones and amputations for compound fractures, which were common and caused by falling off a horse. The diarist Samuel Pepys was ''cut for stone'' in March 1658, and a few months later attended the funeral of a friend who died after being operated on by the same surgeon.[2] The novelist Fanny Burney described the mastectomy she underwent in 1812. The operation lasted seventeen and a half minutes and she could not forbear from screaming with pain throughout. Afterwards, she wrote, ''I saw my good Dr Larry, pale nearly as myself, his face streaked with blood, & its expression depicting grief, apprehension, and almost horrour [sic].''[3] This anecdote serves as an appropriate reminder that the history of animal experiments in the development of anaesthesia is of equal importance as that for the development of surgical technique.

The development of effective sutures, safe anaesthesia, post-operative infection control, open heart surgery, immunosuppression, and modern techniques such as keyhole surgery or operating on the foetus, all depended on 20th century biomedical science and careful animal experimentation.

Anaesthesia

The early history of anaesthesia is poorly documented and hence the subject of controversy.[4] In 1848, Thomas Wakley, founder of *The Lancet*, tested chloroform and ether on a variety of animals. Both were toxic, but more animals died under chloroform than under ether.[5]

Improvements followed in equipment to deliver inhaled anaesthetics, and animal research led to the development of safer mixtures of gases and methods to measure their flow. Nitrous oxide, the

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subject of earlier stories about laughing gas parties, was favoured from the 1860s when it became available in compressed form in cylinders.[6] Humphrey Davy had experimented with the effects of nitrous oxide on cats, and on himself, in the 18th century. In 1920, delivery improved with the invention of the endotracheal tube; the development of further gaseous and volatile liquid anaesthetics followed. Cyclopropane in air was shown to be useful in animals and humans but, like the earlier anaesthetics, it was flammable.[7,8]

The development from the 1950s of modern, non-flammable, safer inhaled anaesthetics depended equally on animal research. Experiments on rodents, rabbits, dogs, cats and monkeys showed that the volatile halothane, mixed with oxygen or air, was easy to use, produced rapid anaesthesia and recovery, had minimal side effects, and had the added advantage of some muscle relaxation. Effective doses of the most widely used modern intravenous barbiturate anaesthetic, thiopentone sodium, were established by research in rats, rabbits and dogs.[9]

Local anaesthetics

Around the same time that nitrous oxide replaced chloroform, rabbit research paved the way for use of cocaine as a local anaesthetic in eye surgery. Intraspinal injection of cocaine in the dog caused numbness of the hind legs, paving the way for use of local anaesthetics for spinal anaesthesia. However, the toxicity of cocaine soon became clear, and around 1900[10] the less toxic procaine was synthesised and widely used until the development of lignocaine in 1948. In tests on rabbit corneas, lignocaine was shown to be more effective and faster-acting.[11] Its low toxicity was established in rodents.

Sutures

Alexis Carrel was the first American to be awarded a Nobel Prize. In his Nobel Prize lecture of 1912, he described how he had developed an effective technique for suturing blood vessels: ''I began to investigate by what means a vascular anastomosis might be effected without producing either stenosis or thrombosis. Many surgeons had previously to myself performed vascular anastomosis, but the results were far from satisfactory....'' He went on to describe his experiments on living cats and dogs and concluded, ''As a result the study of vascular anastomosis can today be considered as completed from the standpoints both of the technique and of the experimental results.''[12] He used extremely fine needles and the thinnest linen thread used by the lacemakers of Valenciennes. He found by experiment that it was important to protect the endothelial layer, obvious today following the discovery of many important factors known to be released by these cells.

Anticoagulants

When John Abel experimented with kidney dialysis in dogs and rabbits around 1915, he prevented coagulation using hirudin[13] extracted from leeches. It was expensive, difficult to extract — early preparations were very impure — caused severe cardiovascular—respiratory side effects and allergic reactions, and was thus unsuitable for human use.

Heparin was first isolated from dog liver and shown to work well during animal studies. It could be extracted in large quantities from beef liver and lung, allowing perfection of purification techniques. In 1937 purified extracts were obtained which were shown to be effective and caused no ill effects in dogs, rabbits, guinea pigs and mice, and subsequently in human patients.[14] Heparin is still prepared from animal sources and each batch is assessed in anaesthetised animals to ensure the absence of substances that may cause hypotension.

Transplantation and immunosuppression

The first human corneal transplant was in 1907 by Zwirn.[1] This followed almost a century of experiments using animals, mainly rabbits. Rejection is rarely a problem because the cornea is not normally vascularised.

Around that time, using his new suturing technique, Carrel found that dog and cat renal autografts were successful.[16] But a kidney transplanted from a different animal of the same species ceased to work after a few days. He therefore concluded that although the surgery worked well, other ''biological factors'' in the host caused changes to the kidney grafted from another animal.

The first kidney transplants leading to long-term survival were dog autografts performed in the 1950s in Boston by Dr Joseph Murray.[17] He also carried out the first human kidney transplant, between identical twins, in 1954.[18]

A development of great significance came in 1959 when Robert Schwartz and William Dameshek

showed, using rabbits, that an anti-cancer drug, 6-mercaptopurine (6-MP), was an immunosuppressant.[19] Roy Calne, then a young surgeon in London, promptly used it in renal transplants between dogs and found they survived for six weeks, six times longer than before. On Sir Peter Medawar's suggestion, he went to Harvard to work with Joe Murray's team. Together, they perfected kidney transplants in dogs, using 6-MP and a new less toxic analogue, azathioprine.[17] They then went on to perform the first successful human unrelated-donor transplant in 1962.

The genetic basis of tissue typing, which ensures the best long-term survival of grafts, was worked out using animals in 1965. Five Nobel prizes (Alexis Carrel in 1912, Peter Medawar in 1960, George Snell in 1980, George Hitchings in 1988, Joe Murray in 1990) were awarded for different aspects of research, mainly on animals, that has assisted the success of transplantation.[18]

Cardiac bypass

Cardiac bypass using an external circulation was first tried with partial success by John Gibbon in the late 1930s using cats. During these early experiments, Gibbon tested various types of pump and oxygenator. He developed an artificial lung based on a spinning hollow cylinder into which the blood was trickled. After World War II, Gibbon and his colleagues started extensive experiments in dogs to test the effects of the prolonged passage of blood through an artificial lung and total exclusion of the heart and lungs from the circulation. Having overcome the problem of multiple small blood clots by installing a fine filter in the circuit, and practicing actual cardiac bypass on the dogs, by the early 1950s the mortality in dogs was down to 12%.[22]

Gibbon performed the first open heart operations using heart lung machines on human patients soon after. The first successful operation was on an 18-year-old girl who had developed right heart failure due to an atrial septal defect.[23] A 45-min operation was performed to correct the defect, the patient made a complete recovery and was recorded as being alive and well 5 years later.

Cold cardioplegia

During these early operations, the heart continued to beat, causing leakage of blood and severe difficulty for the surgeon, presented with a moving target. Experiments using dogs, rabbits and rats established that potassium citrate could be used to safely arrest the heart and that cold cardioplegia would protect it in this state.[24–26]

Replacement heart valves

Serious and established valvular disease was untreatable until the 1950s. From this time there were many attempts to mimic the anatomy of mitral valves using artificial materials. At the same time teams were modifying valves obtained from pigs to prevent rejection. Following work in rabbits, guinea pigs and rats,[27] a biologically inert, functional and durable valve was produced by washing, denaturing and tanning processes. Such valves, usually from pigs, have been used clinically since the 1970s.

Around 1960, Albert Starr developed a simple caged ball valve which, used in dogs, brought survival times of 13 months. These long survival times allowed assessment of the valves' effectiveness and the subsequent need for anticoagulants.[28] The results encouraged Starr to try replacing mitral valves in patients. By October 1961, of the 12 patients who had received artificial mitral valves, two had died from unrelated causes, and three from infections. The remaining patients were well and two had returned to work.

The Bjork–Shiley tilting disk valve was introduced in 1969, and bi-leaflet, pivot designs were introduced in the 1970s.[29]

Minimally invasive surgery

Keyhole surgery was developed in laboratory animals before being tried in humans. For example, young pigs were used to test suturing of bilioenteric anastomoses, which conveyed bile satisfactorily after ligation of the common bile duct.[30]

The 'Parkinson's pacemaker'

By the end of 2004, 30,000 patients around the world with severe, treatment-resistant Parkinson's disease had their lives transformed by an electronic implant that prevents the severe dyskynesia that blight the lives of severely affected patients. The technique is known as deep brain stimulation, or DBS, and involves stimulation of the subthalamic nucleus via a thin-as-a-hair implanted wire powered by a battery-driven microcomputer under the collarbone. DBS has been developed by research

on rhesus macaques and it is impossible to see how these advances could have come about without primate research.[31]

Validity of animal research

The importance of animal research in the historical development of new medicines and surgical approaches cannot be taken as evidence that *all* animal research is valid and readily applicable to human disease, or that alternative approaches should not be sought, or that the use of animals will always be essential.

Animals are likely to continue to be essential in the search to understand and treat the many diseases affecting humans and animals, including newly emerging conditions, but there is no room for complacency. Animal models do not always mimic human disease and there are important and known species differences in response to interventions. For these reasons, there are continued efforts to assess the value of animal research and to develop alternatives.

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